Differentiation of Human Embryonic Stem Cells to Intestinal Fates

Grant Award Details

Differentiation of Human Embryonic Stem Cells to Intestinal Fates

Grant Type: SEED Grant

Grant Number: RS1-00243

Investigator:

Name:	Calvin Kuo
Institution:	Stanford University
Type:	PI

Disease Focus: Intestinal Disease, Metabolic Disorders, Pediatrics, Trauma

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $554,176

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Differentiation of Human Embryonic Stem Cells to Intestinal Fates

Public Abstract:

The roughly 25 feet of intestine in the adult human play numerous essential roles in daily life, such as nutrient absorption, secretion of hormones, and serving as a barrier to infection. Commensurate with these diverse roles, diseases of the intestine are a considerable source of human morbidity and mortality. Indeed, numerous pathologic conditions including inflammatory bowel diseases, mesenteric ischemia, congenital syndromes and trauma, with or without concomitant intestinal resection, all impair intestinal function to the extent that "short-gut" syndromes develop—resulting in effective intestinal failure. Current therapies rely on supportive measures such as total parenteral nutrition, in which patients receive all of their nutrition intravenously, or even intestinal transplantation.

The adult intestine is populated by specialized but highly active intestinal stem cells, which ideally could be harnessed for stem cell therapies of these disabling conditions. However, despite intensive research, no methods currently exist for identifying, isolating, and growing these intestinal stem cells for therapeutic purposes.

Our goal is to develop technologies enabling human embryonic stem (hES) cells to be reliably converted to intestinal cells in culture. Human ES cells can be readily grown in culture but represent a completely undifferentiated tabula rasa. Here, we propose studies to convert hES cells to intestinal stem cells and thence to mature intestinal cells. Towards this goal, we have developed the first methodology to induce intestinal cells to divide and expand as cultures, or "explants" outside of the body. This success has been reliant on the provision in our explants of a nutritive "niche", a specialized area in which signals conductive to intestinal stem cell survival are highly concentrated. In this proposal, the hES cells will be placed in this niche of our explant culture, amidst signals that would promote their conversion from a naïve state into intestinal stem cells and their mature progeny. We will further refine these methods by coaxing hES cells along the first steps towards intestine prior to placing them in the explant niche, as well as by adding hormones to encourage growth of intestinal cells. The use of hES cells could greatly enhance the growth of our explant cultures, vastly expanding the yield of cultured intestine.

The therapeutic applications of this work are clear. The combination of ES cell technology along with our explant culture system holds considerable promise for the eventual generation of large quantities of intestinal stem cells, or even artificial intestine. Hopefully, these will yield effective therapies for the numerous conditions resulting in effective intestinal failure, for which currently available therapies are decidedly suboptimal.

Statement of Benefit to California:

The proposed research will develop new human embryonic stem cell-based technologies enabling the robust propagation of intestinal tissue and its associated stem cells outside of the human body, in laboratory culture. These studies have implications for the treatment of disabling conditions of the intestinal tract including inflammatory bowel disease, mesenteric ischemia and congentital intestinal disorders.
